comprising either an activation domain or a DNA binding domain of a transcription activator and a tester protein having a diversity of at least 1 x 10^7 within the library, the tester protein comprising a first polypeptide subunit whose sequence varies within the library, a second polypeptide subunit whose sequence varies within the library independently of the first polypeptide, and a linker peptide which links the first and second polypeptide subunits;

expressing a target fusion protein in the yeast cells expressing the tester fusion proteins, the target fusion protein comprising either the DNA binding domain or the activation domain of the transcription activator which is not comprised in the tester fusion proteins, and a target peptide or protein; and

selecting those yeast cells in which a reporter gene is expressed, the expression of the reporter gene being activated by a reconstituted transcriptional activator formed by binding of the tester fusion protein to the target fusion protein.

2. (Amended) The method of claim 1, wherein expressing the library of tester fusion proteins includes transforming a library of tester expression vectors into the yeast cells which contain a reporter construct comprising the reporter gene whose expression is under transcriptional control of the reconstituted transcription activator, each tester expression vector comprising

a first transcription sequence encoding either the activation domain or the DNA binding domain of the transcription activator, and

a sequence encoding one of the tester proteins.

4. (Amended) The method of claim 1, wherein the steps of expressing the library of tester fusion proteins and expressing the target fusion protein include causing mating between first and second populations of haploid yeast cells of opposite mating types,

wherein

the first population of haploid yeast cells comprises

a library of tester expression vectors for the library of tester fusion proteins, each tester expression vector comprising

a first transcription sequence encoding either the activation domain or the DNA binding domain of the transcription activator, and

a sequence encoding one of the tester proteins;

the second population of haploid yeast cells comprises a target expression vector comprising

a second transcription sequence encoding either the activation domain or the

DNA binding domain of the transcription activator which is not expressed by the library of tester expression vectors, and

a target sequence encoding the target protein or peptide; and

either the first or second population of haploid yeast cells comprises a reporter construct comprising the reporter gene whose expression is under transcriptional control of the transcription activator.

7. (Amended) The method of claim 1, wherein the diversity of tester proteins in the library of tester fusion proteins is at least $1x10^8$.

8. (Amended) The method of claim 1, wherein the diversity of tester proteins in the library of tester fusion proteins is at least $1x10^{10}$.

9. (Amended) The method of claim 1, wherein the diversity of tester proteins in the library of tester fusion proteins is at least $1x10^{12}$.

10~~14~~. (Amended) The method of claim 1, wherein the first polypeptide subunit in the library of tester proteins comprises an antibody heavy-chain variable region, and the second polypeptide subunit comprises an antibody light-chain variable region.

11~~18~~. (Amended) A method for selecting tester proteins capable of binding to a target peptide or protein, comprising:

(a) transforming a library of tester expression vectors into yeast cells which contain a reporter construct comprising a reporter gene whose expression is under transcriptional control of a transcription activator comprising an activation domain and a DNA binding domain, each tester expression vector comprising

a first transcription sequence encoding either the activation domain or the DNA binding domain of the transcription activator, and

a tester protein sequence comprising first nucleotide sequence encoding a first polypeptide subunit, a second nucleotide sequence encoding a second polypeptide subunit, and a linker sequence encoding a linker peptide that links the first and the second polypeptide subunits;

(b) transforming a target expression vector into the yeast cells simultaneously or sequentially with the library of tester expression vectors, the target expression vector comprising

a second transcription sequence encoding either the activation domain or the

DNA binding domain of the transcription activator which is not expressed by the library of tester expression vectors; and

a target sequence encoding the target protein or peptide;

(c) expressing the tester fusion proteins from the library of tester expression vectors and the target fusion protein from the target expression vector;

(d) selecting those yeast clones in which the reporter gene is expressed, the expression of the reporter gene being activated by binding of the tester fusion protein to the target fusion protein;

(e) isolating the tester expression vector from the selected yeast clones; and

(f) mutagenizing the first and second nucleotide sequences in the isolated tester expression vectors to form a library of mutagenized expression vectors.

---

15 ~~22~~. (Amended) A method for selecting single chain antibodies capable of binding to a human growth factor receptor, comprising:

(a) transforming a library of tester expression vectors into yeast cells which contain a reporter construct comprising the reporter gene whose expression is under transcriptional control of a transcription activator comprising an activation domain and a DNA binding domain, each tester expression vector comprising

a first transcription sequence encoding either the activation domain or the DNA binding domain of the transcription activator, and

a tester protein sequence comprising first nucleotide sequence encoding an antibody heavy chain variable region, a second nucleotide sequence encoding an antibody light chain variable region, and a linker sequence encoding a linker peptide that links the antibody heavy chain and light chain variable regions;

(b) transforming a target expression vector into the yeast cells simultaneously or sequentially with the library of tester expression vectors, the target expression vector comprising

a second transcription sequence encoding either the activation domain or the DNA binding domain of the transcription activator which is not expressed by the library of tester expression vectors, and

a target sequence encoding a human growth factor receptor;

(c) expressing the tester fusion proteins from the library of tester expression vectors and the target fusion protein from the target expression vector; and

(d) selecting those yeast clones in which the reporter gene is expressed, the expression of the reporter gene being activated by binding of the tester fusion protein to the target fusion protein.

Please add the following new claims –

--36. (New) The method of claim 1, wherein the first polypeptide subunit and the second polypeptide subunit are encoded by variable regions of immunoglobulin genes of a human, non-human primates, or rodent.

37. (New) The method of claim 1, wherein the first polypeptide subunit and the second polypeptide subunit are encoded respectively by a heavy-chain variable region and a light-chain variable region of a human immunoglobulin gene.

38. (New) The method of claim 1, wherein the first polypeptide subunit is encoded by a heavy-chain variable region of a first human immunoglobulin gene, and the second polypeptide subunit is encoded by a light chain variable region of a second human immunoglobulin gene different from the first human immunoglobulin gene.

39. (New) The method of claim 18, further comprising:

(g) transforming the library of mutagenized expression vectors into the yeast cells of step (a),

(h) transforming the target expression vector of step (b) into the yeast cells simultaneously or sequentially with the library of mutagenized expression vectors;

(i) expressing the target fusion protein from the target expression vector; and

(j) selecting those yeast clones in which the reporter gene is expressed, the expression of the reporter gene being activated by binding of the tester fusion protein to the target fusion protein.

40. (New) The method of claim 20, wherein the first and second polynucleotides encode an antibody heavy chain variable region and an antibody light chain variable region, respectively.

41. (New) A method for selecting tester proteins capable of binding to a target peptide or protein and improving their binding affinity, comprising:

(a) causing mating between a first and a second population of haploid yeast cells of opposite mating types, wherein

the first population of haploid yeast cells comprises

a library of tester expression vectors for a library of tester fusion proteins, each tester expression vector comprising

a first transcription sequence encoding either the activation domain or the DNA binding domain of the transcription activator, and

a tester protein sequence comprising a first nucleotide sequence encoding the first polypeptide subunit, a second nucleotide sequence encoding the second polypeptide subunit, and a linker sequence encoding a linker peptide that links the first and the second polypeptide subunits;

the second population of haploid yeast cells comprises a target expression vector comprising

a second transcription sequence encoding either the activation domain or the DNA binding domain of the transcription activator which is not expressed by the library of tester expression vectors, and

a target sequence encoding the target protein or peptide; and

either the first or second population of haploid yeast cells comprises a reporter construct comprising the reporter gene whose expression is under transcriptional control of the transcription activator;

(b) expressing the tester fusion proteins from the library of tester expression vectors and the target fusion protein from the target expression vector;

(c) selecting those yeast clones in which the reporter gene is expressed, the expression of the reporter gene being activated by binding of the tester fusion protein to the target fusion protein;

(d) isolating the tester expression vector from the selected yeast clones; and

(f) mutagenizing the first and second nucleotide sequences in the isolated tester expression vectors to form a library of mutagenized expression vectors.

42. (New) The method of claim 41, wherein the mutagenesis is selected from the group consisting of error-prone PCR mutagenesis, site-directed mutagenesis, DNA shuffling and combinations thereof.

43. (New) The method of claim 41, wherein the haploid yeast cells of opposite mating types are $\underline{\alpha}$ and $\underline{a}$ type strains of yeast.

44. (New) A method for selecting single chain antibodies capable of binding to a human growth factor receptor, comprising:

(a) causing mating between a first and a second population of haploid yeast cells of opposite mating types,

the first population of haploid yeast cells comprising

a library of tester expression vectors for a library of tester fusion proteins, each tester expression vector comprising

a first transcription sequence encoding either the activation domain or the DNA binding domain of the transcription activator, and

a tester protein sequence comprising a first nucleotide sequence encoding an antibody heavy chain variable region, a second nucleotide sequence encoding an antibody light chain variable region, and a linker sequence encoding a linker peptide that links the antibody heavy chain and light chain variable regions,

the second population of haploid yeast cells comprising a target expression vector comprising

a second transcription sequence encoding either the activation domain or the DNA binding domain of the transcription activator which is not expressed by the library of tester expression vectors, and

a target sequence encoding a human growth factor receptor; and

either the first or second population of haploid yeast cells comprises a reporter construct comprising the reporter gene whose expression is under transcriptional control of the transcription activator;

(b) expressing the tester fusion proteins from the library of tester expression vectors and the target fusion protein from the target expression vector; and

(c) selecting those yeast clones in which the reporter gene is expressed, the expression of the reporter gene being activated by binding of the tester fusion protein to the target fusion protein.

45. (New) The method of claim 44, wherein the haploid yeast cells of opposite mating types are α and a type strains of yeast. --